REMARKS

Claims 1, 6-11, 14-16, 18, 20, and 25-38 are pending in the application. No amendments have been made by the present response.

35 U.S.C. §102(e) (Anticipation)

At pages 2-5 of the Office Action, claims 1, 6-11, 14-16, 18, and 20-38 were rejected as anticipated by US20030219871.

The Office Action reproduces several lengthy passages selected from different portions of US20030219871. However, the Office Action contains no remarks explaining which portion of the reference is alleged to anticipate the claims. Upon review of the lengthy passages reproduced in the Office Action, there appears to be no reference made in any of these passages to a Chinese Hamster Ovary (CHO) cell comprising an increased amount of Bcl-x_L protein, as is required by the claims. After reproducing portions of the US20030219871 specification, the Office Action concludes the present rejection by stating "[a]lso note the claims." Although CHO cells are mentioned in the claims of US20030219871, there is no indication in the Office Action as to how such disclosure may relate to the claimed subject matter.

An Examiner is required to establish a *prima facie* case of anticipation by pointing out where each and every element of the claimed invention, arranged in the same manner required by the claims, is described identically in a single reference. In re Spada, 911 F.2d 705 (Fed. Cir. 1990). The present Office Action contains no description whatsoever as to where each element of each of the rejected claims is alleged to be found in the cited reference and, as a result, fails to establish a *prima facie* case of anticipation.

In view of the foregoing remarks, applicants request that the Examiner withdraw the rejection of independent claims 1 and 18 and the claims that depend directly or indirectly therefrom.

35 U.S.C. §103(a) (Obviousness)

At pages 5-6 of the Office Action, claims 1, 6-11, 14-16, 18, and 20-38 were rejected as unpatentable over Kim et al. (2000) Biotech. Bioeng. 71:184-93 ("Kim") in view of Mastrangelo et al. (2000) Biotech. Bioeng. 67:555-564 ("Mastrangelo").

According to the Office Action, the difference between Kim and the claimed invention "is that the Cho cells taught by Kim and Lee is stably transfected with Bcl-2, not Bcl-x_L." Applicants respectfully traverse the rejection in view of the following remarks.

Independent claim 1 is directed to a stable cell line comprising a CHO cell comprising an increased amount of Bcl-x_L protein, wherein the cell comprises a first expression vector encoding a secreted protein, and wherein the cell produces an increased amount of the secreted protein as compared to a cell that does not comprise an increased amount of the Bcl-x_L protein. Independent claim 18 is directed to a method of producing a polypeptide in a stable cell line comprising a CHO cell comprising an increased amount of Bcl-x_L protein.

As described in Kim, sodium butyrate can enhance foreign protein expression, but the increased protein expression is compromised by sodium butyrate's cytotoxic effect on cell growth. Kim demonstrates that overexpression of Bcl-2 in CHO cells delays sodium butyrate-induced cell death. According to Kim, increased Bcl-2 expression in the absence of sodium butyrate does not result in increased protein production in CHO cells (see Fig. 10A of Kim). Furthermore, CHO cells contacted with sodium butyrate continue to undergo enhanced apoptosis, though at a delayed rate, even when overexpressing Bcl-2 (see Fig. 10B of Kim). As a result of the cytotoxicity that is associated with sodium butyrate application, Kim does not disclose a stable cell line that overexpresses Bcl-2 and produces an increased amount of a recombinant secreted protein.

According to the final paragraph of the rejection, "it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify Kim and Lee by substituting Bcl-x_L taught by Mastrangelo et al., instead of Bcl-2."

Mastrangelo describes overexpression of Bcl-2 and Bcl-x_L in mammalian cells and the beneficial effect of the overexpression on cell survival in response to cell culture insults. The

Office Action is unclear as to which Mastrangelo publication is relied on in the present rejection. The introductory paragraph of the rejection refers to the Mastrangelo publication of Biotech. Bioeng. 67:555-564. However, the text of the rejection exclusively refers to page numbers that are not contained in this Mastrangelo publication (referring, in order, to pages 545, 547, 546, 549, 550, 551, 552, and 544). If the Office intends to maintain a rejection based upon a Mastrangelo publication, applicants respectfully request that the correct Mastrangelo publication and corresponding page numbers be cited so that applicants may understand the exact nature of the rejection.

As demonstrated in Kim, overexpression of Bcl-2 in CHO cells was not found to result in increased antibody production unless cells were treated with the cytotoxic agent sodium butyrate (which treatment rendered the cells unstable). Nothing in Kim or Mastrangelo would have suggested the unexpected and highly advantageous feature that the inventors of the present application have found to be associated with increased expression of Bcl-x_L in a CHO cell. As detailed in the specification, the inventors have made the unexpected discovery that when Bcl-x_L is expressed in a CHO cell, that cell produces more protein (see specification at page 7, lines 12-14; page 17, lines 16-27; and Fig. 7B). The ability of Bcl-x_L expression to cause a significant increase protein production on a per cell basis (i.e., not simply through increased cell densities via inhibition of apoptosis) makes it particularly advantageous over other apoptosis inhibitors, such as Bcl-2, in recombinant protein production methods. In contrast to Kim's experimental results with Bcl-2, the inventors of the present application unexpectedly found that expression of Bcl-x_L results in increased recombinant protein production without the need for application of the cytotoxic agent sodium butyrate (see Fig. 13 of the present application)

As noted at MPEP 716.02(a), the

> [p]resence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961).

As summarized above, the ability of Bcl-x_L to increase protein production on a per cell basis is a significant unexpected result associated expression of Bcl-x_L in a cell. As a result, Bcl-2 and Bcl-x_L are not merely functional equivalents. Applicants respectfully submit that the presence of this unexpected property, which has not been described as being associated with Bcl-2, is an objective indicator of the nonobviousness of the claimed invention.

In view of the foregoing remarks, applicants request that the Examiner withdraw the rejection of independent claims 1 and 18 and the claims that depend directly or indirectly therefrom.

CONCLUSIONS

Applicants respectfully submit that all grounds for rejection have been overcome and that all claims are now in condition for allowance.

Enclosed is a Petition for Three Month Extension of Time. The extension of time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-036US1.

Respectfully submitted,

Date: July 14, 2010

/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Customer Number 26161
Fish & Richardson P.C.
Telephone: (212) 765-5070
Facsimile: (877) 769-7945